

IN THE UNITED STATES PATENT OFFICE



Application Serial No. 07/675,908

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Applicants: Dr. Rudolf Falk
Dr. Samuel S. Asculai
(Now assigned to
Hyal Pharmaceutical Corporation)

Title: THE USE OF HYALURONIC ACID OR ITS
DERIVATIVES TO ENHANCE DELIVERY
OF ANTINEOPLASTIC AGENTS

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Dr. Samuel S. Asculai

Examiner: Dr. Jacqueline Krikorian Ph.D. (formerly Dr. Stephen Martin,
Ph.D.)

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The Commissioner of Patents
UNITED STATES PATENT OFFICE
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**DECLARATION OF SANFORD H. ROTH
under § 1.132**

I, SANFORD H. ROTH, M.D. of Phoenix, Arizona hereby declare:

1. I obtained my M.D. from Ohio State University, Columbus, Ohio in 1959. I
am presently:

- (a) Medical Director at the Arthritis Centre Ltd. in Phoenix, Arizona;
- (b) Professor ^(adjunct) and Director, Aging Arthritis Program, Graduate School,
Arizona State University, Tempe, Arizona; and

(c) Director, Phoenix Data Bank Network, ARAMIS (American Rheumatism Association Medical Information System).

Now shown to me and marked as *Exhibit 1* is a copy of my Curriculum Vitae.

2. I have been asked to review International Published Application WO 91/04058 (hereinafter referred to as "APPLICATION") which I am advised entered the National Phase in the United States as Application Serial No. 07/675,908, which Application, I am advised, is now owned by Hyal Pharmaceutical Corporation. I am reviewing this patent document as an expert in pharmacotherapeutics, especially related to areas of analgesia, inflammation and immunomodulation.

3. I have assisted Hyal Pharmaceutical Corporation, the Assignee of the above-identified patent application in the U.S. Patent Office as a Consultant. As a Consultant, I was involved in advising Hyal Pharmaceutical Corporation and have carried out research and development and testing for Hyal Pharmaceutical Corporation. I would not, however, let my acting as a Consultant for Hyal Pharmaceutical Corporation or for anyone, interfere with or cloud my professional objectivity and responsibilities in preparing any declaration.

4. I was appointed by the Secretary of Health, Education and Welfare in the United States, 20 years ago, to the Arthritis Advisory Committee of the FDA and that was retained as a liaison to that Committee for the subsequent 20 years. I also became the Chairman of the Anti-rheumatic Drug Guidelines Group to the FDA with industry and the research community over these 20 years. I continue to Chair that Committee in association with its conjunct activities with the International Society for Rheumatic Therapy (ISRT) over the past ten years. I

have been a founder and past-president of the ISRT, which continues to focus on pharmacotherapy and rheumatic diseases. Of the various journals that I am on the editorial board, or reviewer for, I have been associated with DRUGS (ADIS, Auckland, New Zealand), International Board Member for the past 25 years, and on various other international drug publication boards.

5. I have acted as an consultant to both the FDA and the Federal Trade Commission in drug and safety issues and was the expert witness for the Federal Trade Commission in its successful land-mark case against misrepresentation of a topical salicylate therapy in arthritis, testifying before the national administrative court of the United States for the Federal Trade Commission. I continue to consult with both industry and FDA on drug issues. I have been invited to the International League Against Rheumatism.

6. My own experience additionally included a 100-patient double-blinded randomized study of a topical NSAID with placebo control that demonstrated no pharmacotherapeutic difference between placebo and topical NSAID. No topical NSAIDs had heretofore been approved by the FDA for treatment for the pain of arthritis. The issue, however, was of importance since the most utilized group of medications and pharmacotherapy today are the NSAIDs. Over 30 million people use them chronically in the United States alone. These agents in the United States and world-wide account for the overall majority of the more serious adverse toxicity reported to the regulatory agencies and the FDA.

7. I am recognized for introducing into the literature the terminology "NSAID gastropathy" and I continue to contribute to that issue as an expert focusing on the bleeds, perforations, and deaths (up to 10,000 annually in the United States alone) because of agents that can compromise the gastroprotective defenses of the stomach. This happens most frequently in the very elderly at

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sustained higher dosage. This pharmacokinetics and pharmacodynamics are both important in relation to this. The elderly, 65 and older are the most frequent NSAID user group susceptible to NSAID gastropathy and its complication. Because NSAID gastropathy is not conveniently associated with upper gastrointestinal warning symptoms, the majority of dangerous gastrointestinal bleeds are silent. This problem is a public health dimension costing the United States economy over \$3,500,000,000 annually and resulting in an estimated 10,000 deaths yearly from NSAID use associated gastrointestinal bleeds.

The focus of various textbooks on arthritis therapy that I have published to date (three as author and eight as contributing author) has been on pharmacotherapy as it relates to rheumatic diseases.

In addition to 30 years of clinical experience in pharmacotherapy, I have been a principal investigator with virtually every non-steroidal inflammatory drug (NSAID) in research in the United States. I have also acted as a consultant and principal investigator related to monoclonal antibody therapy in rheumatoid arthritis (RA), cyclosporine therapy in RA and various other immunomodulators.

I continue to consult with both industry and the FDA on drug issues. I was elected to the prestigious Committee of Revision of the United States Pharmacopeia (U.S.P.) for the past eight years as well as World Health Organization discussions on anti-inflammatory analgesic and anti-rheumatic drug therapy held in Geneva. I was invited to speak before the Arthritis Advisory Committee specifically to the issue of topical NSAIDs as an expert witness.

8. I have had experience as a principal investigator and consultant related to work with topical hyaluron (HA) acting as a vehicle for diclofenac in analgesia and in arthritis now known as hyanalgesic-D (HA-D), a product of Hyal Pharmaceutical Corporation, the Assignee of this Patent Application which I am examining. I have published and presented this work on HA-D at national and international meetings.

Accordingly, such a topical delivery system as HA-D for NSAID would not have systemic or direct gastric toxicity thus offering gastrosparring and systemic safety. Since previous topical NSAID delivery systems have failed to meet efficacy requirements of the United States Food and Drug Administration (FDA), the desirability of such an agent that could be effective and well-tolerated is evident.

9. Accordingly, as Chairman of the International Board and International Confidential Meeting in Israel, in 1992 (a confidential meeting of Hyal Pharmaceutical Corporation's employees and consultants), I first became aware of the work with topical hyaluron preparation in combination with diclofenac. That initial work had shown documented activity against precancerous skin lesions. I have subsequently become involved as a consultant to the research development of such a preparation and principal investigator in a major placebo controlled, randomized, double-blinded study in osteoarthritis. I have presented a paper before the European League Against Rheumatism (Amsterdam, Netherlands, July, 1995) that demonstrated the formulation had significant activity and excellent tolerance and the data in the paper has subsequently been presented before the FDA at a pivotal study. As a consultant to a series of international meetings in Toronto; Geneva, Switzerland; and Paris, France over these past three years I have shared in the clinical and basic research that provides us state-of-the-art advances in understanding the role of hyaluron (HA)

as an active carrier for various therapeutic agents.

10. Furthermore, dramatic developments include understanding of the active targeting role of HA in topical absorption, penetration, and targeting of hyaluron receptors in the epidermis as well as parenteral use in targeting of hyaluron lymphatic and vascular expression receptors. These are related to vascular neoplasia and the immunopathy. These latter areas are not only of importance in cancer and vascular restenosis clinical states, but also in rheumatic and connective tissue disease. These latter disorders can now be immunomodulated by targeting immunologically active agents including chemotherapeutic agents and monoclonal antibodies to such disease specific target areas.

11. Thus, the new information regarding HA as a carrier for an NSAID such as diclofenac (HA-D) in a topically applied formulation without the potential for NSAID gastropathy and other common NSAID toxicities such as renal dysfunction and electrolyte disturbance is now being documented.

12. My principal areas of expertise and focus related to International Published Application WO 91/04058 that I have reviewed and issued patents and publications which I was asked to review (U.S. Patent 4,736,024, U.S. Patent 4,808,576, U.K. Patent 769,287 and an article entitled "Hyaluronic Acid: Its Structure and Use") relate to HA, our present state of knowledge of HA, its biological activities, targeting potential, adjunctive depot role in association with various pharmacological agents, and how that may affect the bio-availability, efficacy, and pharmacokinetic characteristics of those agents. This includes safety and dosage issues.

13. All drugs have a therapeutic ratio at which their efficacy is recognized. Pharmacologically this is only acceptable if toxic side effects and intolerance are

not evidenced at or above this dosage level. Host characteristics will mitigate the efficacy and safety of an agent as pharmacodynamics are influenced by age and other co-morbid and co-medication features.

14. Thus, as an example, the most utilized group of medications in pharmacotherapy today are the NSAIDs. Over 30 million people use them chronically in the United States alone. These agents in the United States and world-wide account for the overwhelming majority of the most serious adverse toxicities reported to the regulatory agencies and the FDA.

I am recognized for introducing into the literature the recognition of NSAID gastropathy and continue to contribute to that issue as an expert focusing on the bleeds, perforations, and deaths (up to 10,000 annually in the United States alone) because of agents that can compromise the gastroprotective defenses of the stomach. This happens most frequently in the very elderly at sustained and higher dosages. Thus, pharmacokinetics and pharmacodynamics are both of importance in relation to this.

15. Furthermore, those 65 years and older, are the most frequent group susceptible to NSAID gastropathy and are also the most common users of NSAIDs in the population. Because NSAID gastropathy is not conveniently associated with gastric upset symptoms and the majority of dangerous gastrointestinal bleeds are silent and occur without warning symptoms, the problem has been recognized of public health dimension. Accordingly, a topical delivery system for NSAID that would not have systemic or direct gastric topical toxicity would be desirable.

16. To date, previous topical systems have failed to meet characteristics that the United States FDA has set forth such approval. I have not only participated

in those discussion processes as recorded in the federal registry of the Arthritis Advisory Committee, but have been asked to speak to them specifically as an expert. I am, therefore, especially interested in the new level of information regarding HA as a carrier for NSAID such as HA-D without the recognized risk of NSAID gastropathy and, indeed, other common NSAID toxicities, especially renal dysfunction.

17. The basis for activity of HA-D has now been determined by recognition of the referral of pain model. Type C pain fibers, substance P, and local pain receptors deter the role of the epidermis as part of the signal system for pain. HA receptors in the epidermis can act as a depot for topical HA-D. This provides a basis for "shedding" HA-Ds, a system that now sustains analgesia through a continuing pharmacologic delivery system. This is now being confirmed and peer-review published. Separate from the usual testimonial examples of the patents I have reviewed, HA has properly documented, cross-sectional experiences. Case examples are useful, as long as there is a body of data that can properly confirm, and not reject, the observations offered. For example, information of HA targeting specific immunological and vasoactive receptors, including RHAMM and ECAM provide a basis for understanding the lymphatic and immune system targeting that is seen with HA.

18. Separately from this, I have worked as a principal investigator of dimethyl sulfoxide (DMSO). I have testified as a liaison expert to the FDA Arthritis Advisory Committee meetings on DMSO. This interesting agent is a major penetrator of the dermis. Indeed, it is the only pharmacologically active substance recognized that can immediately penetrate the barrier of the dermis and become systemic. As such a unique pharmacologic agent that has also been shown to have the degrees of analgesia and potential for local healing effects as in burns, use in combination with HA (see Schultz, U.S. Patent 4,808,576) is

totally confounding when trying to interpret: (1) penetration effects, (2) analgesia, (3) models for anti-inflammatory effects. Therefore, the discussions in the Schultz Patent are thoroughly flawed because of that association and I believe must be scientifically rejected as too confounded for interpretation of understanding of pharmacactivity of HA itself, as I discuss in the next section.

19. Approaching previous patents dating back to the mid-1950s reminds us of how much the state of the art has changed. As a pharmacotherapist, clinician, and scientist, I approach the teachings of a patent "Application" with a perspective aside from those skills required of the legal profession. For to me, "teaching" implies a basis in previous knowledge and learning. That knowledge base necessarily changes over the years. Therefore, what might have been regarded as appropriate teaching at an earlier time may or may not stand up as valid under present scrutiny. This because those teachings and examples adequate for patent "Application" appear to be limited to empirical untested testimonial examples.

20. Correct observations, when adequately documented, can indeed continue to be accepted, but better understood decades later. Others, in retrospect, may simply be early simplistic observations that actually teach away from that which we now should understand from their application and use. In reviewing the pertinent patent applications relative to this declaration, it is useful to remind ourselves of that evolution toward correct state of the art.

21. An example in point is the determination that HA has now been well characterized as a glycosaminoglycan or mucopolysaccharide. It is far more than a macromolecular space³ structurally. Indeed, these previously recognized properties have been demonstrated as cosmetically useful in the vitreous humor and the epidermis.

22. However, in the case of the articular joint, it is important to recognize that when the natural HA of the joint is degraded by hyaluronidase, and associated inflammatory factors, in the presence of inflammation or infection the actual rheology of the joint is changed. That can be threatening to the articular cartilage.

23. A more current development, however, is the present understanding of HA as a carrier to site target pharmacologically active agents as taught by the Application. A case in point is the recent work in respect of HA-D (HA in combination with NSAID). Appropriate randomized double-blinded, placebo controlled study has demonstrated the analgesic efficacy of this combination. Furthermore, 70 percent of the HA epidermal receptors will be saturated with HA-D after a week of this topical application allowing a depot release of HA-D in the epidermis (as distinguished from the formulation itself).

24. Thus, we have more recently internationally reported a blinded study of 90 patients in which HA-D was able to reduce from usual four times daily application to less frequent daily applications after one week of use. The majority documented continuing benefits after one month. Furthermore, after blinded placebo substitution, a sustained effect of analgesia could be documented for several weeks or longer. This formulation is, I am advised, Formulation 3 of International Publication WO 93/16732 and WO 93/16733 which each entered the National Phase in the United States as a Continuation-in-Part Application of U.S. Application Serial No. 07/675,908, the "Application" of concern herein.

25. This then confirms our present understanding of HA at actively penetrating and targeting epidermal receptors and acting as a carrier for diclofenac (which itself only has a two hour half life). The sustained analgesia

resulting corroborates the depot effect in the skin (not the formulation itself) this creates, allowing sustained shedding of the pharmacotherapeutically active NSAID.

26. In the discussion that follows, the Application teaches suitable molecular weight prepared forms of HA having a molecular weight average of from 150,000 daltons to 750,000 daltons to achieve such effect. This effect is part of a dynamic process of delivery as taught in the Application. These are pharmaceutically acceptable non-toxic salts since in-vivo the HA is not in acid form. Further, no depolymerized HA preparation achieves this effect (see U.K. Patent 769,287 to Seifter) and no additional carrier agent such as dimethyl sulfoxide (DMSO), which is an analgesic, is required. The transport is active and targeting. State-of-the-art science confirms a basis for these controlled observations.

27. The teachings in the Application are, in contrast to the earlier patents of Schultz, etc. of the agent "spreading" not being focused for delivery to a site. The agent is diluted as it spreads not delivered to the site in need of treatment. This is an example of an undocumented empirical observation without understanding of mechanisms and that later scientific study will refute. Furthermore, U.S. Patent 4,736,024 provides a formulation which, when dosage amounts are take and applied, provide an adhesive film to the eye with a retard effect (see column 1, lines 47-53).

28. Having read the said document, International Publication No. WO 91/04058, I have concluded that the inventors, Drs. Falk and Asculai, have discovered and disclosed the use of dosage amounts comprising effective dosage amounts of medicines and/or therapeutic agents together with specified amounts of forms of hyaluronic acid for transporting (delivering) the medicines and/or therapeutic agents to underperfused tissue and/or pathological tissue.

The specified amounts of the form of hyaluronic acid in the dosages alters the distribution and performance of the medicines and therapeutic agents in the body and produces an unusual targeting for the underperfused tissue and/or pathological tissue (see p. 24, lines 13-17) of International Publication No. WO 91/04058.

29. Thus, the invention does not relate to the mere combining of known medicines and therapeutic agents with hyaluronic acid; the invention of International Publication No. WO 91/04058 relates to the use of the form of hyaluronic acid for targeting the medicines/therapeutic agents for better performance. By using the forms of hyaluronic acid with medicines and their therapeutic agents that would be known or may become known in the future to persons skilled in the art for the treatment of a disease or condition then, if the said medicines or therapeutic agents are useful for the treatment of said disease or condition, then, according to the inventors, the medicine/therapeutic agent is effectively transported to the site in the body where the treatment is needed to target the medicine or therapeutic agent, as the case may be, to the site of the disease/condition in need of treatment.

30. Would persons reading said International Publication No. WO 91/04058 have sufficient information and teaching in the document to enable them to so use the invention? In my professional opinion, they would, having regard to the teachings in International Publication No. WO 91/04058. The dosage amounts can be administered in the usual method for example, intravenously, intra-arterially, intraperitoneally, intrapleurally, transdermally, on the skin (topically), rectally, orally, or by direct injection for example, into a tumour, abscess, or similar disease focus, or put on a patch to be secured to the skin of the patient (p. 18, lines, 2-7). Persons skilled in the art would understand the routes of administration so specified.

31. In my opinion, persons skilled in the art would be highly skilled and would have a full understanding of drugs and medicines used in, for example, the disease or condition being treated such as cancer treatment and, therefore, would be capable of interpreting the pharmacological data in International Publication No. WO 91/04058.

32. There might well be aspects that are not immediately understood or recalled by such persons skilled in the art. However in such circumstances such persons skilled in the art with the qualifications specified would have the professional capacity and would also have the basic scientific education necessary to seek the required information and understanding from standard known textbooks and other known sources.

They would also know the terms used in the Application for example, such as, "calcium channel blockers" which includes nifedipine which is mentioned at p. 35, line 23 with reference to sub-paragraph 16 of the said International Publication No. WO 91/04058.

33. Such persons skilled in the art would also understand that the varying doses of 10 mg. to 1,000 mg. of the form of hyaluronic acid per 70 kg. person are those which work with the optimal doses tending to range between 50 and 350 mg. of hyaluronic acid per 70 kg. person (see p. 26, lines 33-34).

34. With respect to molecular weights used of hyaluronic acid, I refer to p. 29, lines 34-35 of International Publication No. WO 91/04058 which discloses the use of a 15 ml. vial of sodium hyaluronate, 20 mg./ml. being a 2% solution, the solution being prepared to present hyaluronic acid in sterile water with a mean average molecular weight of about 225, 000 daltons. The hyaluronic acid used

referred to at page 30 of the Application may have a molecular weight range of 150,000 to 225,000 daltons. At page 31, another amount of hyaluronic acid is specified at line 33-34 as a viscosity average molecular weight less than 750,000 daltons.

35. The specification of International Publication No. WO 91/04058 also provides, at page 33, line 29, that where high molecular weight hyaluronic acid (or salts or other forms thereof is used), the high molecular weight hyaluronic acid must be diluted to permit administration to the patient to ensure no intramuscular coagulation.

36. Having regard to the teachings with respect to molecular weight, I have determined from the teachings of International Publication No. WO 91/04058 that persons skilled in the art would experience no difficulty in preparing the dosages useful for treating the disease or condition which they are desirous to treat. The hyaluronic acid dosage amounts prepared from the hyaluronic acid exemplified in the teachings of the patent are not highly viscous and would, in my opinion, be diluted by persons skilled in the art for several reasons before use in administering to the patients. The dilution of the hyaluronic acid would be clearly understood by persons skilled in the art. The first reason for diluting is for forming the dosages containing the drug. The second reason would be to avoid high immediate concentrations of drug in the blood stream which also governs the rate of infusion. Thirdly, dilution would be carried out by persons skilled in the art to ensure smooth flow into the venous line where the dosage was to be administered intravenously. The volume and rate of intravenous infusion would be decided to accord with standard practice for intravenous infusions.

37. International Publication No. WO 91/04058 specifies molecular weights of

hyaluronic acid having a mean average molecular weight range between 150,000 to 750,000 daltons in the exemplified samples of hyaluronic acid. The patent specifies that higher molecular weight amounts of hyaluronic acid for example, those disclosed at page 32, line 25 to page 33, line 24 may be suitable provided that where the high molecular weight hyaluronic acid is used, the hyaluronic acid must be diluted to permit administration and ensure no intramuscular coagulation (p. 33, lines 29-31).

38. The details given in International Publication No. WO 91/04058 are sufficiently clear to enable a qualified practitioner to adopt the methodology without undue experimentation and achieve the results therein.

39. The Application also speaks to hyaluronic acid and/or salts. Hyaluron exists in-vivo in either acid or salt form as can be implied from the Application ("A") and the literature. That these salts are pharmaceutically acceptable and non-toxic is evident from the safety of the various examples in International Publication No. WO 91/04058 and scientific literature and the need therefore for patient treatment.

40. International Publication No. WO 91/04058 does teach the use of HA with doses relative to treatment. Examples include the use indomethacin, on pages 52-53 (Cases XVIII and XIX), ranging from 100 to 300 mg, dissolved in HA 300 mg. In both cases, the doses of NSAID indomethacin is elevated or excess to that normally taken. 100 mg. is also excessive but the 100 mg. dosage amount was tolerated in the patient of Case XIX because the side effects were not present in that patient. From Case XVIII, the patient appeared to better tolerate the amount of indomethacin of 300 mg. in the dosage form. On page 25, 200 mg of HA was used with 1 to 2 mg per kilogram of indomethacin dissolved in methyl glucamine per kg. of patient. On this same page, 50-200 mg of NSAID -

hyaluronic acid are referred to as combined (50 mg. NSAID and 200 mg. of HA). This includes examples of reduction in side effects for this dose of indomethacin above compared to use with the HA combination. The NSAID dosage in combination with HA is thus associated with reduced side effects.

41. The object, or end-point, of treatment taught in International Publication No. WO 91/04058 is that HA confers an active carrier targeting role. That allows for the more specific effect of the agent potentially reducing side effects. All agents have side effects. They are side effects in that they are not the desired effect. One targets HA to a specific organ or receptor such as vascular endothelial cell receptors or monoclonal antibody receptors in the lymphatics. The pharmacoactive agent is more effectively delivered and targeted for an enhanced therapeutic ratio. This would especially be true when less of a pharmacotherapeutically agent would be necessary to achieve the desired efficacy.

42. All active pharmacotherapeutic agents have a therapeutic ratio. That ratio implies that both efficacy thresholds and adverse toxicity are usually dose related. When the efficacious dose can be safely delivered well below the toxic dose, that agent can be made safer under those conditions of use (i.e., targeted use).

43. Although I am not an expert in the treatment of cancer, I am an expert in the use of the chemotherapy of agents used in cancer since the same agents are used in rheumatic diseases (i.e., cyclosporine, methotrexate, etc.). The same principles of safety in targeting and monoclonal antibody expression hold true. The protective microvasculature, endothelial cell migration properties and issues of lymphoplasia are common issues in both cancer and rheumatic disease expression. International Publication No. WO 91/04058 teaches the use of HA carrier for targeting pharmacotherapeutic agents and gives sufficient examples to provide a basis for other formulations without the requirement for any undue

experimentation

44. International Publication No. WO 91/04058 teaches that the usual molecular weight of HA has been characterized as not homogenous, and not unimolar, and represents an average ranging from the source of that specimen and the methodology. It could range from 150,000 daltons to 750,000 daltons. The Viscosities are proportional to molecular weight. The viscosity would be relevant for an intra-articular preparation because of affect on rheology of the synovial fluid. However, viscosity does not appear to be relevant to penetration of the skin by HA or delivery systemically particularly when persons skilled in the art in respect of delivery would dilute the HA to form dosages (as a matter of routine) and compositions from which the dosages are taken. International Publication No. WO 91/04058 also does refer to dosages relative to primary systemic administration as a carrier. It also indicates the safety potential for the targeting carrier role. International Publication No. WO 91/04058 is relevant to cancer, just as it is to arthritis. The dosages, both amounts of, and molecular weights of, HA given in the "Application" is noted to be non-toxic. Thus, no undue experimentation is required because persons skilled in the art would know to dilute a viscous high concentration amount of HA to form the required dosages.

45. The teachings of the Application indicate that various pharmacotherapeutic agents can be used with HA for various clinical purposes. The delivery of the pharmacotherapeutic agent would be a co-feature of the carrier use of HA. Topical HA for NSAID (HA-D) versus a parenteral HA for chemotherapeutic and other agents, to be delivered for systemic use.

Examples include an HA delivery system for an NSAID such as indomethacin or diclofenac. This can avoid the gastric mucosal toxicity of oral

delivery of that NSAID by topical application of HA-D, which avoids systemic exposure. Parenteral targeting to receptors as discussed in the "Application WO 91/04058" allows indomethacin to be better tolerated for systemic use. The Application emphasizes the enhancement of the dosing advantages of such targeting effect as discussed earlier.

47. The West reference to which I was referred on the effect of hyaluronate and its metabolism in regulation of angiogenesis, is confounding in the face of the newer knowledge of HA targeting and controlling endothelial cell migration factors. West has been downplayed in the scientific community - even doubted.

48. Application WO 91/04058 speaks to various doses of pharmacotherapeutic agents to be used with HA as a carrier. We have spoken to the issue of the therapeutic ratio, favorably influenced by such carrier targeting effects.

49. We have discussed the advantages of 200 mg of HA in combination with indomethacin (on page 25 of the International Publication No. WO 91/04058) as an example of the issue of therapeutic ratio as it applies to "dose excess." This is therefore implicit to that discussion. Targeting of NSAID is given as an example of reducing side effects and is also previously discussed in detail. Previous "other HA patent claim references" are reviewed in association with these considerations (enclosure).

50. In summary, International Publication No. WO 91/04058, in my opinion, appropriately presents to persons skilled in the art the use of HA as a carrier for topical and systemic application. The basis for the safety and efficacy benefits are now being documented. Previous "other HA patent" teachings were not a reference to the development of yhr teachings expressed in International Publication No. WO 91/04058's as the teachings of International Publication No.

WO 91/04058 have been shown to teach something different - a broad basis confirming the unique role for HA for delivery of medicines and therapeutic agents. Where medicines and agents are suitable for use to treat a condition or disease, their delivery to the focus (site) of the disease or condition is enhanced by the use of HA.

51. I now turn to review the various other HA patent documents as they may relate to the invention of International Publication No. WO 91/04058 that has been discussed in detail and inherent in the following summary of the invention of International Publication No. WO 91/04058.

A dosage form of a pharmaceutical composition of a therapeutic agent in combination with HA (including salts) which is characterized to be in a dosage form suitable for humans and containing an effective dosage of the therapeutic agent and an effective amount of HA to penetrate the site based upon nontoxic transport by HA. HA is a bio-administered topically or systemically by the dosage used and the amount of HA is sufficient to provide a therapeutic dosage of HA >10 mg/70 kg person and the molecule weight of HA is $< 750,000$ daltons and above 150,000 daltons. The invention also includes the method of administering these dosages to treat diseases or conditions by delivering the therapeutic agent to the site in need of treatment for the disease or condition.

On the basis of the above, the other HA patent documents are reviewed in reference to their teachings. Whether these teachings are alone or in combination, they do not achieve the teachings of International Publication No. WO 91/04058 or the above paragraph.

52. Della Valle, et al. (U.S. Patent 4,736,024) which does specify that quantities of HA (fractions or salts) for medicament containing agents or medicines without specifying specific dosages of latter except for drops that are microlitres and contain < 1 mg. HA (see column 27, line 57, column 30, line 37, column 31, line

52, and column 33, lines 23-24). At column 30, lines 65-68, Della Valle teaches that the film formed on the eye releases the pilocarpine and takes no part in the delivery being but a stable film on the cornea:

"Transcorneal penetration of pilocarpine seems therefore to depend on the capacity of hyaluronic acid to vehicle the drug forming a homogenous and stable film on the cornea."

This is consistent with the teachings at column 1, lines 46-53.

53. Della Valle does not teach specific to chemotherapy issues of minimum dosages of 10 mg of HA to deliver effective therapeutic agent and does not appropriately discuss the effects of molecular weight of HA. More importantly, Della Valle does not teach transport or delivery; their use of HA is passive. Nor does Della Valle teach the use of >200 mg of HA in order to deliver the therapeutic agent for purposes of reducing side effects. There is discussion specific to an effect that simply could be described as "sticking to the eye" of HA with also a spacer role of HA and discussion of various types of other agents without appropriate dosage, delivery, targeting, or toxicity considerations. Della Valle includes no adequate definition of combination therapy for understanding transport receptor targeting or issues that would alter therapeutic agent dosage to below side effect levels depending upon amount and bio-availability through HA delivery mechanism specific to topical or parenteral route. Della Valle does not provide delivery or targeting. Nor do their dosages work that way.

54. Seifter, U.K. Patent 769,287 discusses a spreading effect (like hyaluronidase) provided by its PDHA (partially depolymerized HA). The spreading effect cannot, according to Seifter, be achieved with HA (undepolymerized). Additionally, Seifter causes a spreading effect with PDHA which causes dilution not delivery or

targeting of the site in need of treatment.

55. Schultz, et al. (U.S. Patent 4,808,576). Schultz teaches no delivery of medicine or therapeutic agents. Schultz uses HA as the therapeutic agent when administered systemically and the body transports it all over by the bodily functions. Topically, Schultz requires a transdermal carrier. Without the carrier, HA will not work topically (see column 12, lines 14-17). Schultz assumes that higher viscosities are convenient for topical application and lower viscosities for intravenous administration. This simplistic observation is not consistent with the present state of knowledge.

56. Schultz is seriously confounded (doubted) by including DMSO in examples with use. DMSO is a unique spreading agent that absorbs through topical tissues immediately and has unique characteristics of its own, including analgesic properties. That confounds HA use and confounds interpreting the role of HA in Schultz. It is, therefore, not only inappropriate, but interferes with any meaningful understandings from teachings in Schultz, which are thus seriously flawed.

57. Although Schultz claims HA will "reduce the sequelae" of trauma, the basis for this is not specified. This is further confounded by discussions of a polysulfated glucose amino glycan (Arteparon). This is supposed to stimulate bio-synthesis of HA. The "direct use" of HA is spoken of in terms of molecular weights that are "too large" to be "transferred" to mammalian tissues, not consistent with state-of-the-art knowledge.

The clinical examples given, including Freund's adjuvant arthritis induced in horses, is ill-advised since this includes both acute and chronic inflammatory models of inflammation. They are not specified separately. The

reported clinical results are, therefore, confounded as examples of HA therapy. Further confounding is the caution for "no more HA than is necessary" to be "prudent." This is unscientific. It is not based upon our present knowledge of dose-relationship bio-delivery systems with HA.

58. The very vague statements about "joint distress" have no scientific value in interpreting "remote application" of parenteral HA. The various examples given are not appropriate to those issues. The confounding effect of DMSO in the examples further invalidates the usefulness. It teaches away from the proper understanding of HA use. Thus, if Schultz's teachings are to be considered rigorously we would have to reject that they provide any basis for use alone or in combination with other HA patents such as Seifter (U.K. Patent 769,287) and/or Della Valle (U.S. Patent 4,736,024).

59. Therefore, I declare that, in summary, my expert opinion is that International Publication No. WO 91/04058 teaches appropriate use and application of HA and its broad range of delivery of therapeutically active agents as previously reviewed. These teachings of the Application have been corroborated. Furthermore, they are being supported by continuing basic and clinical research studies into the HA delivery of the various therapeutic agents. The successful use of these agents in the clinical conditions described under double-blinded, placebo-controlled, rigorous studies now reported in the international literature and to the medical community further corroborate and validate the teachings of International Publication No. WO 91/04058. The teachings are not found in the prior art. They are totally unexpected.

60. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that

willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 24 day
of August, 1996.



SANFORD H. ROTH

EXHIBIT 1

CURRICULUM VITAE

SANFORD H. ROTH, M.D.

PERSONAL

Date & Place of Birth: 6/12/34, Ohio

Marital Status: Married, 2 daughters

CURRENT POSITIONS

Medical Director, Arthritis Center, Ltd., Phoenix, Arizona
Professor and Director, Aging and Arthritis Program, Graduate
School, Arizona State University, Tempe, Arizona

Director, Phoenix Data Bank Network, ARAMIS (American Rheumatism
Association Medical Information System)

EDUCATION

B.S., Ohio State University, Columbus, Ohio, 6/55

M.D., Ohio State University, Columbus, Ohio, 6/59

POSTGRADUATE TRAINING AND RESEARCH EXPERIENCE

Arthritis Public Health Service Traineeship, USPHS Grant, Ohio
State University, 3/59-7/59

Arthritis and Rheumatism Foundation Research and Traineeship Grant,
Ohio State University, Rheumatology Department, 7/59-12/59

Intern, Mt. Carmel Hospital, Columbus, Ohio, 7/59-6/60

Fellow, Mayo Graduate School of Medicine, Rochester, Minnesota,
7/62-7/65 (certificate in Internal Medicine and Rheumatology)

Mayo Foundation Fellowship Grant, Department of Physiology, Mayo
Foundation Graduate School, University of Minnesota, 7/63-7/64
(Analysis of Serotonin and Histamine and related Enzyme Systems
in Synovial Fluid and Tissue)

MILITARY SERVICE

Captain, USAF Medical Corps, Department of Medicine, Sheppard Air
Force Base, Texas, active duty, 7/60-7/62

LICENSURE

Arizona #4427, 5/65

Minnesota #16415, 10/63

PROFESSIONAL ACTIVITIES

Private practice, limited to rheumatology, 7/65 - present

Consultant, Arthritis Advisory Committee, United States Food and
Drug Administration, 1982 -

Liaison Arthritis Representative of the American Society of
Clinical Pharmacology and Therapeutics to the Arthritis Advisory
Committee, United States Food and Drug Administration, 1983-86

Consultant, United States Food and Drug Administration Office of
Compliance, 1986 -

Rheumatology Consultant, U.S. Federal Trade Commission, 1980 -

PROFESSIONAL ACTIVITIES. (continued)

Director, Arthritis Rehabilitation Program, St. Luke's Medical Center, Phoenix, Arizona, 1980-87
Secretary-General, International Society for Rheumatic Therapy, 1988-90
Vice President (President-Elect), International Society for Rheumatic Therapy, 1990-92
President, International Society for Rheumatic Therapy, 1992 -
Rheumatology Consultation, Veteran's Administration Medical Centers, 1970 -
Consultant, Arthritis Foundation Clinics
Rheumatology Consultant, Ciba-Geigy Pharmaceuticals, 1983-
Rheumatology Consultant, 3M/Riker Laboratories, Inc., 1981-89
Rheumatology Consultant, Boots Pharmaceutical Company, 1980-87
Rheumatology Consultant, Bristol-Myers, 1984
Rheumatology Consultant, Upjohn Laboratories, 1985
Rheumatology Consultant, Pennwalt Pharmaceuticals, 1986
Rheumatology Consultant, Hoffman-LaRoche, Inc., 1986
Rheumatology Consultant, Greenwich Pharmaceuticals, 1986
Rheumatology Consultant, Searle Laboratories, 1987-90
Rheumatology Consultant, SmithKline Beecham, 1990 -
Rheumatology Consultant, Glaxo Pharmaceuticals, 1991 -
Rheumatology Consultant, Angelini Pharmaceuticals, 1992 -
Chairman and Moderator, Senior Adult Continuing Education Lecture Series for the Arthritis and Aging Program, College of Public Programs, Arizona State University, Tempe, Arizona - 1985 -
Moderator, Wellness and Self Care ITFS Series, Arizona State University, Tempe, Arizona, 1985
Visiting Scholar in Rheumatology, Beijing Medical College, Beijing, China, 10/82-11/82
Preceptor, Visiting Chinese Scholar Program for Arthritis, Phoenix, United States-China Education Institute, 2/82 -
Chairman, Clinical Trials Committee, Pan American League Against Rheumatism (PANLAR), 1987 (4-Year Term, Re-elected 1990)
Liaison Representative, PANLAR Clinical Trials Committee to ILAR Clinical Research Committee, 1987 (4-Year Term, Re-elected 1990)
Committee of Revision, U.S. Pharmacopeial Convention, 1990 -
Chairman, Antirheumatic Drug Development Group, 1982 -
International League Against Rheumatism/World Health Organization Antirheumatic Drug Development Task Force, 1991 -
Professor & Consultant, Beijing Medical College Arthritis Center, 1992 -

SOCIETY AND COMMITTEE MEMBERSHIPS

St. Luke's Hospital & Medical Center, Phoenix, Arizona
Member, CME Committee, 1985
Member, Medical Committee, 1985
Director, Arthritis Rehab Program, 1980-87
Member, Physician's Council

SOCIETY AND COMMITTEE MEMBERSHIPS. (continued)

Harrington Arthritis Research Center, Phoenix, Arizona
Co-Founder
Executive Committee, 1983 -
Board of Trustees, 1983-88
Medical Research Director, 1983-88
Scientific Research & Education Committee, 1986 -
Arthritis Foundation
Member, Medical and Scientific Committee, 1967 -
Chairman, Medical and Scientific Committee, 1967-72
Central Arizona Chapter Board Member, Executive Board, 1967-72
American Rheumatism Association/American College of Rheumatology (ACR)
Founding Fellow
Therapeutic and Drug Committee, 1979-84; 1987-
Ad Hoc Committee on Future Meeting Sites, 1983-85
Glossary Committee, 1981-84
Co-Chairman, Western Regional Chapter, 1977
Committee on Clubs and Councils, 1977
Liaison Committee to Regional Medical Program, 1974-76
Co-Director, ARAMIS (Medical Information Systems)
Director, Phoenix Data Bank Network
ARA Computer Committee
Chairman, Anti-inflammatory Drug Study Club, 1974-84
Chairman, New Drug Guidelines Group for Antirheumatic Drugs, 1974 -
Lupus Foundation of America, Board Member, 1981 -
Medical Advisory Board, Greater Arizona Chapter
American College of Physicians Regional Program Committee, Annual
Philip S. Hench Lectureship Chairman, 1978-79
Chairman, Council on Arthritis in Arizona, 1968-70
Chairman, Governor's Conference on Arthritis in Arizona, 1967
Maricopa County Medical Society
Rehabilitation Committee
American Society of Clinical Rheumatology
Past President, Executive Council, Founding Member
Fellow, American Society of Clinical Pharmacology and Therapeutics
American Medical Association
American Society of Internal Medicine
Mayo Clinic Alumni Association
Secretary, Mayo Clinic Fellows Association, 1964-65
President, Mayo Clinic Fellows Rheumatology Society, 1964-65
Director, Mayo Clinic Film Society, 1964-65
Philippine Rheumatology Association (honorary)
Argentine Rheumatology Society (honorary)
Member of Hyal International Research Committee
MISCELLANEOUS
Who's Who in the West, Marquis Publications, Chicago, 1983 - present
Best Doctors in the United States, Seaview Publications, New York,
1983 - present
Who's Who in America, Marquis Publications, Chicago, 1987

Who's Who in Finance and Industry, Marquis Publications, Chicago, 1987

MISCELLANEOUS, (continued)

Who's Who in America, Marquis Publications, Illinois, 1990-94.
Who's Who in the West, Marquis Publications, Illinois, 1994-95.

PUBLICATIONS

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4. Roth SH: Double-blind evaluation of a new indole in the treatment of rheumatoid arthritis. Arth and Rheum 12:328, 1969 (Abstract).
5. Roth SH, Sun DC, Englund DW: Esophageal abnormalities of rheumatoid arthritis. Arth and Rheum 14:182, 1971 (Abstract).
6. Roth SH: Painless arthrocentesis of the knee. Hosp Physician 9(5):67, 1973.
7. Roth SH: Arthritis Therapy: New drugs offer major alternatives. Hosp Physician 9(11):70, 1973.
9. Harris BK, Chapman B, Roth SH, et al: Quantitative study of doctor-patient communication in rheumatic diseases. AZ Med 30:262-3, 1973.
10. Roth SH: Safety and efficacy of Naprosyn therapy in rheumatoid arthritis patients with upper gastrointestinal dysfunction. Naprosyn in the treatment of rheumatic diseases. Proceedings of symposium, London, 1973. Syntex Pharmaceuticals Ltd; 5(4):20, 1974.
11. Roth SH: Evaluation of sudoxicam in rheumatoid arthritis. Excerpta Medica, 1974.
12. Roth SH, Booth G: An open trial of naproxen in rheumatoid arthritis patients with significant esophageal, gastric and duodenal lesions. J Clin Pharm 15(4/2):378-84, 1974.
13. Roth SH: Treatment of arthritis complicated by upper gastrointestinal tract disease, Scand J Rheum 4(Suppl 8), 1975.

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15. Roth SH, Englund DW, Harris BK, Ross HG: Tolmetin with acetaminophen in the treatment of rheumatoid arthritis. Excerpta Medicus 9:112-21, 1975.
16. Roth SH: The corticosteroid sparing effect of tolmetin. Excerpta Medicus 9:148-59, 1975.
17. Roth SH: Search for new agents in arthritis therapy. AZ Med 33(4):278-81, 1976.
18. Roth SH: Anti-inflammatories: Exploring new options. Current Prescribing 2(5):46-9, 1976.
19. Roth SH: The new anti-inflammatories: How they stack up to RA therapy. Drug Topics 120:56-7, 1976.
20. Roth SH, Englund DW, Harris BK: Long term fenoprofen therapy in patients with rheumatoid arthritis. J Rheum 3(Suppl 2):43-8, 1976.
21. Roth SH, Ehrlich GE: Can we cure arthritis after all? Current Prescribing 2(11):41-6, 1976.
22. Roth SH: Rheumatoid arthritis: Long term therapy with tolmetin sodium. Ortho Digest 4:16-24, 1976.
23. Roth SH: Costs of monitoring chrysotherapy. AZ Med 31(4):250-1, 1977.
24. Kaye R, Roth SH, et al: Naprosyn (naproxen) in practice: No. 1 in a series of regional round tables conducted at University of California Medical Center, San Francisco, July 1976. Syntex Pharmaceuticals, Inc., May 1977, p. 1054.
25. Blechman WJ, Roth SH, Lord A, et al: Experience with naproxen in treating osteoarthritis. Geriatrics 32(7):72-82, 1977.
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30. Roth SH: Benoxaprofen: Once a day vs. twice a day in patients with rheumatoid arthritis or osteoarthritis. J Rheum 7(Suppl 6):68-75, 1980.
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34. Roth SH: What role rheumatology? (editorial) Arch Intern Med 142(1):27, Jan 1982.
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42. Roth SH: The team care approach to arthritis. Arthron 1(4):2-6, 1982.

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70. Roth SH: Nonsteroidal anti-inflammatory drug gastropathy. We started it - can we stop it. Arch Intern Med 146:1075-76, June 1986.

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72. Roth SH: Arthritis therapy: Back to the future (editorial) Arch Intern Med 147(1):36-7, 1987.
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76. Roth SH: NSAID-induced gastropathy: A rheumatologist's point of view. J Musculoskeletal Med; 4(Suppl. 3):21-24, 1987.
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79. Roth S: What is new in arthritis therapy: Back to the future. Arch Intern Med; 147:37-7, 1987.
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83. Roth SH: Some things old are new again. Western J Med, p. 4, Sept 1987.
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89. Roth SH: NSAIDs and gastropathy: A rheumatologist's review. J Rheumatol 15:912-919, 1988.
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91. Roth SH: Pharmacologic approaches to musculoskeletal disorders. Clin Geriatr Med 4(2):441-61, 1988.
92. Roth SH: Nonsteroidal anti-inflammatory drugs: Gastropathy, deaths and medical practice. Ann Intern Med 109(5):353-4, 1988.
93. Graham DY, Agrawal NM, Roth SH: Prevention of NSAID-induced gastric ulcer with misoprostol: Multicenter, double-blind, placebo-controlled trial. Lancet 2(8623):1277-80, 1988.
94. Roth SH: Rethinking rheumatic disease therapy. J Rheumatol 16(11):1408-9, 1988.
95. Roth SH: Antiulcer therapy in NSAID gastropathy: A rheumatologist's perspective. Drug Info Journ 22, 1988.
96. Roth SH: Conspectus: Nonsteroidal anti-inflammatory drug gastropathy. Comprehensive Therapy 14(2), Feb 1988.
97. Roth SH: NSAIDs: Risk-benefit versus cost-benefit. Drug Inform J 22:477-81, 1988.
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99. Roth SH: NSAIDs and gastropathy: A review for rheumatologists. J of Rheum, June 1988.

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100. Zautra AJ, Okun MA, Robinson SE, Lee D, Roth SH, Emmanuel J: Life stress and lymphocyte alterations among patients with rheumatoid arthritis. Health Psychol 8(1):1-14, 1989.
101. Roth SH: Cost/benefit medicine, red flags and fibrositic work scales (letter). Arch Intern Med 149(3):721, 1989.
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103. Roth SH: Merits and liabilities of NSAID therapy. Rheum Dis Clin NA 15(3):479-98, 1989.
104. Roth SH, Agrawal N, Mahowald M, Montoya H, et al: Misoprostol heals gastroduodenal injury in patients with rheumatoid arthritis receiving aspirin. Arch Intern Med 149(4):775-779, April 1989.
105. Roth SH: Prevention of NSAID-induced gastric mucosal damage and gastric ulcer: A review of clinical studies. J Drug Dev 1(4):255-63, Sept 1989.
106. Roth SH: Rethinking rheumatic disease therapy, J Rheum 16(11), 1408-9, 1989.
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111. Roth SH: Long-term studies are key to understanding and preventing NSAID gastropathy. Perspectives on Pain. Vol 1, No 1, 1-10, 1991.
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121. Caldwell JR, Roth SH, and the Naproxen EC Study Group: A Double Blind Comparing the Efficacy and Safety of Enteric Coated Naproxen to Naproxen in the Management of NSAID Intolerant Patients with Rheumatoid Arthritis and Osteoarthritis. The Journal of Rheumatology 1994; 21:689-95.
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124. Roth SH: Role of the Rheumatologist in 1995: Leadership (Editorial). The Journal of Rheumatology, 1995. Vol.22, No.1.

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125. Roth SH, Bennett RE, Caldron PH, et al: Endoscopic Evaluation of the Long Term Effects of Diclofenac Sodium and Naproxen in Elderly Patients with Arthritis. Clinical Drug Investigation, 9(3):171-179, 1995. Adis International.
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131. Roth SH: Patients and Classification Criteria (letter to editor). The Journal of Rheumatology, Volume 22, Number 7, 1995. -- 1435.
132. Roth SH: Future of Rheumatology: New Directions?. Journal of Rheumatology (Publication Pending)
133. Roth SH: NSAID Gastropathy: A New Understanding. Archives of Internal Medicine (Publication Pending)

BOOKS

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2. Roth SH: "Interaction of Drug Therapy on the Rehabilitation Process and Management of Rheumatic Disease" in Rehabilitation Management of Rheumatoid Conditions, Ehrlich GE (ed), Williams and Wilkens, Philadelphia, 1981.

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3. Roth SH: "Dosing of Flurbiprofen in Rheumatoid Arthritis and Osteoarthritis" in Progress in Rheumatology, Machtey I (ed), Wright-PSG Publishing, Boston, 1982.
4. Roth SH: "Nonsteroidal Anti-inflammatory Drugs" in Rheumatoid Arthritis, Utsinger PD, Ehrlich GE, Zvaifler NJ (eds), J.B. Lippincott Co., Philadelphia, 1984.
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8. Rheumatic Therapeutics, Roth SH (chief ed), McGraw-Hill, New York, 1985.
9. Roth SH: "Salicylates" in Rheumatic Therapeutics, McGraw-Hill, New York, 1985.
10. Roth SH: "Drug Therapy and the Rehabilitation Process: A Necessary Interaction: in Rehabilitation Management of Rheumatoid Conditions, Second Edition, Ehrlich GE (ed), Williams and Wilkins Publishers, Philadelphia, 1986, pp. 88-106.
11. Roth SH: "Salicylates" in Management of Rheumatic Disease, Katz WA (ed), J.B. Lippincott, Philadelphia, April 1988.
12. Roth SH: "Antiarthritic Drugs" in AMA Drug Evaluations, Sixth Edition, American Medical Association, Chicago, 1986 (consultant).
13. Roth SH: "Pharmacologic Approaches to Musculoskeletal Disorders in the Elderly" in Clinics in Geriatric Medicine, Hammerman DA (ed), Vol. 4, #2, May 1988, pp. 441-61.
14. Roth SH, Bennett RE: "Nonsteroidal Anti-inflammatory Drug Gastropathy: Old Disease, New Name", in Swabb/Szabo: Ulcer Disease: Investigation and Basis for Therapy, 5:123-147, Marcel Dekker, 1991.
15. Roth SH, Bennett RE, Caldron PH: "Rheumatoid Arthritis" in Difficult Medical Management, W.B. Saunders Company, 1991, pp. 586-597.

BOOKS (continued)

16. Roth SH, Bennett RE: "NSAIDs, Peptic Ulcer, Esophageal Disease, and Gastropathy" in Therapeutic Applications of NSAIDs: Subpopulations and New Formulations, Marcel Dekker, Inc, New York, 1992.

EDITORIAL ACTIVITIES

1. Medical Contributing Editor, Medical Economics Publications
RISS, Hospital Physician, 1960-68
Current Prescribing, 1976-80
2. Honorary International Consulting Editor, ADIS International Drugs, 1977 -
3. Editor-in-Chief, Arthron, Continuing Professional Education Division of Sieber & McIntyre, Inc., 1982-85
4. International Editorial Board Member, Medical Progress, ADIS Publications, 1984 -
5. Review Board Member, Archives of Internal Medicine, 1984 -
6. Editor, Arthritis and the Gut Series, Practical Gastroenterology, 1984 -
7. Editor-in-chief, RHEUMATIC THERAPEUTICS, McGraw-Hill, 1985
8. Review Board Member, Arthritis & Rheumatism, 1986 -
9. Editorial Board Member, Comprehensive Therapy, 1987 -
10. Editorial Advisory Board Member, VA Practitioner, 1987 -
11. Editorial Board Member, Journal of Drug Development, 1987 -
12. Editorial Consultant, Perspectives in Rheumatology, 1988
13. Editorial Board Member, Practical Gastroenterology,
14. International Editorial Board, Inpharma, Adis International, 1992 -
15. Consultant and Reviewer, Digestive Diseases & Sciences, 1992 -

MEETINGS AND PRESENTATIONS

1. "Preliminary long-term multi-dosage evaluation of auranofin in rheumatoid arthritis". Presented at the 4th Congress of the Southeast Asia and Pacific Area League Against Rheumatism (SEAPAL), Manila, Philippines, January 1980.
2. "A double-blind comparison of isoxepec and indomethacin in rheumatoid arthritis". Presented at the 4th SEAPAL Congress, Manila, Philippines, January 1980.
3. "Long term safety experience with naproxen in GI-compromised rheumatoid arthritis patients". Presented at the 4th SEAPAL Congress, Manila, Philippines, January 1980.
4. Panel Moderator, "Arthritis therapy: Controversy and change". American Society of Clinical Pharmacology and Therapeutics, San Francisco, March 1980.
5. Host/Chairman, American Society of Clinical Rheumatology Annual Meeting, Phoenix, March 1980.
6. "Arthritis drug toxicities: Recognition and reversal". Presented at the Understanding Arthritis Symposium of the American Society of Clinical Rheumatologists Annual Meeting, Phoenix, March 1980 (proceedings published).
7. Guest Lecturer, "Extra-articular manifestations of rheumatoid arthritis" and "What to do when aspirin fails". 40th Annual Western Colorado Springs Clinic, Grand Junction, Colorado, April 1980.
8. "Compliance: The bottom line" panel on "Decision making in the treatment of rheumatoid arthritis". Chairman, Anti-inflammatory Drug Study Group, Annual Scientific Meeting, American Rheumatism Association, Atlanta, May 1980.
9. "American Rheumatism Association Medical Information Survey (ARAMIS) of treatment of arthritis in the elderly". Presented at the VI International Congress on Rheumatic Diseases, Aix-les-Bains, France, June 1980.
10. Panel Participant, "Research, treatment and understanding arthritis". Arthritis Foundation conference, San Diego, September 1980.
11. "The salicylate quandary: Adverse drug reactions and interactions". Presented at the Prostaglandins, Platelets and Salicylates Symposium, New Orleans, November 1980.

MEETINGS AND PRESENTATIONS (continued)

12. Panel Moderator, "Salicylates in the treatment of rheumatic disease". Presented at the Second International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, November 1980.
13. "Dosing of flurbiprofen in rheumatoid arthritis and osteoarthritis". Presented at the Second International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, November 1980.
14. Panel Participant, "Can remission be induced in rheumatoid arthritis?". Second International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, November 1980.
15. Invited faculty lecturer, "Drug interaction in the patient with rheumatoid disease". CME program (video-tape), Hahnemann Medical College and Hospital, Philadelphia, December 1980.
16. Moderator, "Emerging role of remittive drug therapy". Anti-inflammatory Drug Study Group, American Society of Clinical Pharmacology and Therapeutics Meeting, New Orleans, March 1981.
17. Program chairman, "New horizons and controversy in arthritis therapy", Anti-inflammatory Drug Study Group, St. Luke's Hospital Arthritis Program, Scottsdale, April 1981.
18. Program Chairman, "Oh, my aching back (A pain in the neck)", St. Luke's Hospital Arthritis Program, Scottsdale, April 1981.
19. "Comparison of pulse methotrexate therapy with gold salt therapy in rheumatoid arthritis". Presented at the 45th annual meeting, American Rheumatism Association, Boston, June 1981.
20. "Acid peptic disease in the anti-inflammatory therapy of arthritis". Presented at the 45th annual meeting, American Rheumatism Association, Boston, June 1981 (proceedings published).
21. Panel Participant, "A comparison of benoxaprofen and sulindac in patients with rheumatoid arthritis and osteoarthritis". Benoxaprofen Symposium, 15th International Congress of Rheumatology, Paris, June 1981.
22. "Data bank comparison of single versus combined anti-inflammatory drug therapy in arthritis". Presented at the 15th International Congress of Rheumatology, Paris, June 1981.
23. "Double-blind evaluation of cimetidine therapy of UGI disease in arthritis". Presented at the 15th International Congress of Rheumatology, Paris, June 1981.

MEETINGS AND PRESENTATIONS (continued)

24. Panel participant, "Experience with levamisole using one day per week treatment for rheumatoid arthritis". Immunoregulatory Therapy in Rheumatoid Arthritis Symposium, 15th International Congress of Rheumatology, Paris, June 1981.
25. "Ibuprofen treatment of arthritis patients with active upper GI and/or nonsteroidal anti-inflammatory drug intolerance". Presented at the 15th International Congress of Rheumatology, Paris, June 1981.
26. "New directions in flurbiprofen dosage". Presented at the 15th International Congress of Rheumatology, Paris, June 1981.
27. "Remission: The goal of rheumatic disease therapy". Presented at Therapeutic Innovation in Rheumatoid Arthritis: Worldwide Auranofin Symposium, Montreal, October 1981.
28. Panel Moderator, "Arthritis: Insight, mechanism and treatment". American Academy of Physical Medicine and Rehabilitation, San Diego, November 1981.
29. Program Chairman, "New Directions in Arthritis Therapy", New Directions in Arthritis Symposium, University of Massachusetts Medical School, Worcester, November 1981.
30. "Salicylates: From revolution to evolution". Presented at the New Directions in Arthritis Symposium, University of Massachusetts Medical School, Worcester, November 1981.
31. "The management problems of arthritis therapy". Presented at St. Francis Hospital, University of Hawaii, Honolulu, February, 1982.
32. Chairman, "The long road to success". Wonewok Rheumatology Seminar, Minnesota, March 1982.
33. "Determination of acid peptic disease in arthritis and double-blind evaluation of cimetidine therapy". Presented at the 83rd annual meeting, American Society of Clinical Pharmacology and Therapeutics, Florida, March 1982 (proceedings published).
34. "Comparative clinical studies of benoxaprofen, indomethacin, naproxen and sulindac in rheumatoid and osteoarthritis. Presented at the New Perspectives in Chronic Arthritis and Its Pharmacologic Management Symposium, San Francisco, April 1982 and New Orleans, May 1982.
35. "A clinical interpretation of laboratory tests in arthritis". Presented at the annual meeting, Arizona State Society of Medical Technology, Phoenix, May 1982.

MEETINGS AND PRESENTATIONS (continued)

36. "Understanding lupus and related misunderstandings". Presented at the annual meeting, Arizona State Society of Medical Technology, Phoenix, May 1982.
37. Chairman/Moderator, "Arthritis: Today's progress, tomorrow's changes", St. Luke's Hospital Arthritis Program, Phoenix, June 1982.
38. "Zero order release aspirin (Zorprin): A new approach to salicylate therapy". Presented at the VIII Pan American Congress of Rheumatology, Washington, D.C., June 1982.
39. Moderator, "The long road to success in arthritis therapy", VIII Pan American Congress of Rheumatology, Washington, D.C., June 1982.
40. Participant, "Drug treatment of rheumatic diseases" forum. Rheumatic Diseases: An Integrated Approach to Total Patient Care, Frankfurt, Germany, September 1982.
41. "Arthritis and Aging". Presented for St. Luke's Hospital Clinical Gerontology course, Phoenix, October 1982.
42. Chairman, "Rheumatology today: A Self assessment" symposium. St. Paul and Captiva Island, January 1983.
43. "What can and what has been done to return aspirin to the list of modern anti-inflammatory drugs". Presented at the International Symposium on Recent Advances in the Pharmacology of Rheumatic Disorders, Bermuda, February 1983.
44. Participant, Auranofin Investigator's meeting, Philadelphia, March 1983.
45. Participant, ARAMIS/Data Bank Network Seminar, Palo Alto, California, March 1983.
46. Chairman, "The truth about rheumatism and arthritis: Hype versus hope", A David C.H. Sun Memorial Institute Seminar, Scottsdale, March 1983.
47. "Arthritis: Drug intervention". Presented at the Third Annual Congress of the National Association of Orthopaedic Nurses, Reno, May 1983.
48. "NSAIDs and fenoprofen's pro-drug mode of action". Presented at the SEAPAL meeting, Bangkok, Thailand, June 1983.

MEETINGS AND PRESENTATIONS (continued)

49. "The role of the pharmaceutical industry in arthritis patient care". Presented at the Lederle Symposium on Rheumatic Diseases: The Patient and the Community, Marbella, Spain, September 1983.

50. International organizer, Third International Seminar on the Treatment of Rheumatic Diseases, Israel, November 1983.

51. Panel Moderator, "Anti-inflammatory therapy and acid peptic diseases: Problems and prevention", Third International Seminar on the Treatment of Rheumatic Diseases, Israel, November 1983.

52. "Structure-activity relations in aspirin alternative agents". Presented at the Third International Seminar on the Treatment of Rheumatic Diseases, Israel, November 1983.

53. Panel Member, Ciba-Geigy Arthritis Advisory Committee, Palm Springs, California, December 1983.

54. "Rheumatic diseases: Therapeutic technology, today and tomorrow". Presented at the SEAPAL meeting, Bangkok, Thailand, January 1984.

55. "Methotrexate (MTX) low dose pulse therapy in rheumatoid arthritis". Presented at the 12th annual meeting, American Rheumatism Association Western Regional Chapter, Tucson, February 1984.

56. Moderator/Chairman, "New anti-inflammatory drug guidelines" workshop at the 85th annual meeting, American Society of Clinical Pharmacology and Therapeutics, Atlanta, March 1984 (proceedings published).

57. "How to treat rheumatic disease and still spare the stomach". A David C.H. Sun Memorial Institute Symposium, Gastroenterology for Clinicians, Scottsdale, March 1984.

58. Fenbufen Symposium, Lisbon, Portugal, April 1984.

59. "New face on salicylates". Presented at the annual meeting, American Society of Clinical Rheumatology, Florida, April 1984.

60. Panel Member, "Nonsteroidal anti-inflammatories with special reference to gastrointestinal effects". Annual meeting, American Society of Clinical Rheumatology, Florida, April 1984.

61. Chairman/Moderator, "Arthritis, old age - What you can do". A David C.H. Sun Memorial Institute Symposium, Sun City and Scottsdale, May 1984.

MEETINGS AND PRESENTATIONS (continued)

62. "An introduction to arthritis and present understandings of therapy". A David C.H. Sun Memorial Institute Symposium, Sun City and Scottsdale, May 1984.
63. "Safety studies of anti-inflammatory alternatives in arthritis therapy". Presented at the European League Against Rheumatism (EULAR) Symposium, Regensburg, Germany, September 1984 (proceedings published).
64. "NSAIDs: Is longer lasting better?". Presented at workshop on Lysine Acetylsalicylate-Aspegic, Illinois, September 1984.
65. Chairman/Moderator, "Arthritis and the elderly". A David C.H. Sun Memorial Institute Symposium, Sun City and Scottsdale, October 1984.
66. Liaison consultant, U.S. Food and Drug Administration Arthritis Advisory Committee meeting, Washington, D.C., October 1984.
67. Participant, Voltaren Symposium, Jamaica, November/December 1984.
68. Chairman/Moderator, New Antirheumatic Drug Guidelines meeting, Scottsdale, January 1985.
69. Chairman/Moderator, Lectures series on Aging and Arthritis sponsored by the College of Public Programs, Arizona State University, Tempe, Arizona, January through May 1985 (series of 14 lectures).
70. Chairman/Moderator, "Proposed guideline changes for drug approval with special reference to antiarthritic agents". 86th Annual ASCPT meeting, San Antonio, March 1985.
71. Participant, ARAMIS meeting, San Francisco, March 1985.
72. Report on the new antirheumatic drug guideline recommendations, Arthritis Advisory Committee meeting, U.S. Food and Drug Administration, Bethesda, Maryland, April 1985.
73. Chairman/Moderator, "The adverse drug reactions of arthritis therapy: Choices and responses". International League Against Rheumatism (ILAR) meeting, Sydney, Australia, May 1985.
74. Chairman/Moderator, New Antirheumatic Drug Guidelines Group International Workshop, ILAR meeting, Sydney, Australia, May 1985.
75. Chairman/Moderator, "The terrible twosome: NSAIDs and ulcers". Clinical program seminar at the 49th annual ARA meeting, Anaheim, California, June 1985.

MEETINGS AND PRESENTATIONS (continued)

76. Participant, New Antirheumatic Drug Guideline Review Group, Antirheumatic Drug Committee of the ARA, 49th Annual ARA meeting, Anaheim, California, June 1985.
77. Host/Chairman, "How to treat arthritis and spare the stomach". Post-ARA associated symposium, Anaheim, California, June 1985.
78. Moderator, "NSAID-induced peptic gastropathy". American Society of Clinical Rheumatology meeting, Greenbrier, West Virginia, August 1985.
79. Program Coordinator, "Drug induced gastritic - can we break the cycle?". 54th Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Vancouver, September 1985.
80. Moderator, "Arthritis Therapy and GI Disease". 37th Annual meeting of the American Academy of Family Physicians, Anaheim, California, October 1985.
81. "Drug toxicity of nonsteroidal anti-inflammatory therapy". Presented at the International Mayo Alumni Meeting, Rochester, Minnesota, October 1985.
82. Participant, Carprofen Investigator's Meeting, New York, October 1985.
83. Moderator, NSAID Induced Gastropathy: Our Disease?, Ft. Lauderdale, Florida, January 1986 and September 1986 (sponsored by the Southern Medical Association).
84. "NSAID-induced gastropathy". Presented at the Houston Rheumatology Society meeting, Houston, Texas, February 1986.
85. "NSAID-induced gastropathy". Presented at the Vancouver Medical Society meeting, Vancouver, Canada, February 1986.
86. "Research and new developments in arthritis". Presented for the Dupont Lecture Series, March 1986 in Sun City and Mesa, Arizona.
87. ARAMIS Investigators meeting, Palo Alto, California, March 1986.
88. ITFS Lecture Series (Interactive Television Fixed Services). A seven lecture series. Co-sponsored by Arizona State University, March through May 1986.
89. Chairman/Moderator/Speaker, Rheumatic Therapeutics Symposium, Scottsdale, Arizona, May 1986.

MEETINGS AND PRESENTATIONS (continued)

90. Chairman/Moderator, New Antirheumatic Drug Guidelines Group meeting, Scottsdale, Arizona, May 1986.
91. "Long term sucralfate therapy in patients with nonsteroidal anti-inflammatory drug induced gastrointestinal side effects" poster presentation, American Rheumatism Association annual meeting, New Orleans, June 1986.
92. Moderator, Current Issues in Rheumatology, Post-ARA associated symposium, New Orleans, June 1986.
93. Participant, Rioprostil Investigator meeting, Cape Cod, Mass., June 1986.
94. "Current rationale for anti-inflammatory therapy in arthritis". Presented at Du Centre Hospitalier Privé "La Roserie", Paris, France, July 1986; University Hospital, Ghent, Belgium, July 1986; Aktuelle Rheumatologie, Bayreuth, Germany, August 1986.
95. Panelist, Therapies in Rheumatology, American Osteopathic College of Rheumatology meeting, Las Vegas, November 1986.
96. "Endoscopic comparison of the tolerance and safety of carprofen and ibuprofen in patients with rheumatoid arthritis", poster presentation at IX Pan American Congress of Rheumatology (PANLAR) meeting, Buenos Aires, Argentina, November 1986.
97. Co-Chairman, Rheumatic Therapeutics Update symposium, IX Pan American Congress of Rheumatology (PANLAR) meeting, Buenos Aires, Argentina, November 1986.
98. Liaison Consultant, U.S. Food and Drug Administration Arthritis Advisory Committee meeting, Bethesda, Maryland, December 1986.
99. "Efficacy of nabumetone in osteoarthritis". Presented at New NSAIDs - Criteria for Therapeutic Selection symposium, San Diego, California, December 1986.
100. "NSAID-induced gastropathy: A rheumatologist's point of view". Presented at the American College of General Practitioners in Osteopathic Medicine and Surgery meeting, Scottsdale, Arizona, March 1987.
101. Chairman, NSAID Therapy: Emerging Clinical Concerns. Wonewok, Minnesota, March 1987.
102. Chairman and Moderator, Rheumatic Therapeutics Symposium, Scottsdale, Arizona, April-May 1987.

MEETINGS AND PRESENTATIONS (continued)

103. "Misoprostol heals aspirin-induced gastropathy in rheumatoid arthritis". Presented at Clinical Perspectives on Misoprostol: Peptic Ulcer Disease and NSAID-Induced Gastropathy. Digestive Disease Week, Chicago, May 1987.

104. "NSAID gastropathy: A rheumatologist's perspective". Presented at Cytoprotection, NSAIDs and the Arthritic Patient. La Costa, California, May 1987.

105. "Effects of misoprostol on aspirin-induced gastropathy". Presented at Cytoprotection, NSAIDs and the Arthritic Patient. La Costa, California, May 1987.

106. "Misoprostol heals aspirin-induced gastropathy in rheumatoid arthritis". (poster presentation). American Rheumatism Association meeting, Washington, D.C., June 1987.

107. Chairman, "Gastropathy and Arthritis Therapy", post-American Rheumatism Association seminar, Washington, D.C., June 1987.

108. "NSAIDs and the stomach: Endoscopy in arthritis". Presented at the Department of Rheumatology, University of Manchester, Manchester, United Kingdom, June 1987.

109. "Misoprostol mitigates serious aspirin-induced gastropathy despite continuing use of aspirin in rheumatoid arthritis". Presented at the XIth European Congress of Rheumatology, Athens, Greece, June-July 1987.

110. "Endoscopy controlled study of the safety of nabumetone versus naproxen in arthritis therapy". (poster presentation). XIth European Congress of Rheumatology, Athens, Greece, June-July 1987.

111. "New directions in arthritis therapy". Presented at Campinas University, Campinas, Brazil, August 1987.

112. "NSAID therapy: Emerging clinical concerns". Presented at the 50th Argentine Society of Rheumatology meeting, Buenos Aires, Argentina, August 1987.

113. "New directions in arthritis drug therapy". Presented at the 50th Argentine Society of Rheumatology meeting, Buenos Aires, Argentina, August 1987.

114. "Therapeutic approaches - A rheumatologist's view". Presented at Effects and Side Effects of NSAIDs, Canadian Rheumatism Association satellite meeting in conjunction with the Royal College of Physicians and Surgeons of Canada, Winnipeg, Canada, September 1987.

MEETINGS AND PRESENTATIONS (continued)

115. Chairman/Moderator: NSAID-Induced Gastropathy: Our Disease. Ft. Lauderdale, September 1987.
116. "A comparative endoscopic study of osteoarthritis and rheumatoid arthritis patients treated with nabumetone versus naproxen". Presented at New Nonsteroidal Anti-inflammatory Drugs: Criteria for Therapeutic Selection, (Moderator, session on Efficacy of nabumetone in Osteoarthritis), San Diego, California, December 1988.
117. "Socioeconomic impact of NSAID gastropathy". Presented at the National Congress of Rheumatology, Puebla, Mexico, February 1988.
118. "Antiulcer therapy in NSAID gastropathy: A rheumatologist's perspective". Presented at the Drug Information Association Workshop on Cost/Benefit of Pharmaceutical Products, Hilton Head, South Carolina, March 1988.
119. "NSAIDs: Risk benefit versus cost benefit". Presented at the Drug Information Association Workshop on Cost/Benefit of Pharmaceutical Products, Hilton Head, South Carolina, March 1988.
120. Participant, ARAMIS Data Bank Network Symposium, Palo Alto, California, March 1988.
121. Participant, Geigy Medical Lecture Series, "Safety issues with NSAIDS - update". Presented in Laguna Niguel, California in March 1988 and San Diego, California in May 1988.
122. "Treatment of aspirin-induced ulcers in rheumatoid arthritis patients continuing on ASA therapy". Presented at NSAID-Induced Gastropathy: Treatment and Prevention. Madrid, Spain, May 1988.
123. Participant, U.S. Food and Drug Administration Arthritis Advisory Committee, Bethesda, Maryland, May 1988.
124. Participant, "Digestive Diseases in Seniors: An International Health Forum", Digestive Disease Week, New Orleans, May 1988.
125. "NSAID Gastropathy", presented at "Digestive Diseases in Seniors: An International Health Forum", Digestive Disease Week, New Orleans, May 1988.
126. Chairman, Antirheumatic Drug Study Group meeting, 52nd Annual American Rheumatism Association Meeting, Houston, Texas, May 1988.
127. Chairman/Moderator, Rimadyl Investigator's Meeting, Houston, Texas, May 1988.

MEETINGS AND PRESENTATIONS (continued)

128. Co-chairman, 2nd Congress of the International Society for Rheumatic Therapy, London, June 1990.
129. Chairman, Rheumatic Therapeutics Symposium, Scottsdale, AZ, April 1991.
130. Visiting Guest Professor, Korean Rheumatism Association Meeting, Seoul, May 1991.
131. Participant, Progress in Arthritis Therapy: Nabumetone Investigator's Meeting, Philadelphia, June 1991.
132. Chairman, NSAID Gastropathy Section, EULAR, XIIth European Congress of Rheumatology, Budapest, June-July 1991.
133. "Misprostol with NSAID Therapy", presented at EULAR, XIIth European Congress of Rheumatology, Budapest, June-July 1991.
134. Participant, American Osteopathic Association National Convention "Nonsteroidal Anti-inflammatory Drug Use in the Elderly: Perspectives for the Family Practitioner" Symposium, New Orleans, November 1991.
135. Chairman, Antirheumatic Drug Development Guidelines Meeting, Washington, D.C., May 1992.
136. Co-Chairman, 3rd International Congress of the International Society for Rheumatic Therapy, Mannheim, Germany, May 1992.
137. "Endoscopy Study of the Effects of Nabumetone, Ibuprofen and Concomitant Ibuprofen/Misoprostol on Osteoarthritis Patients", presented at the American College of Rheumatology Annual Meeting, November 1992, Atlanta, Georgia.
138. "Comparative Endoscopic Evaluation of Elderly Osteoarthritis Patients Treated with Choline Magnesium Trisalicylate Versus Piroxicam", presented at the American College of Rheumatology Annual Meeting, November 1992, Atlanta, Georgia.
139. "Nizatidine May Prevent NSAID-Associated Peptic Ulceration in High Risk Osteoarthritis Patients", presented at the American College of Rheumatology Annual Meeting, November 1992, Atlanta, Georgia.
140. "Double-Blind Esophageal Gastroduodenoscopy in Controlled Study of Diclofenac Versus Naproxen in the Elderly with Rheumatoid and Osteoarthritis", presented at the American College of Rheumatology Annual Meeting, November 1992, Atlanta, Georgia.

MEETINGS AND PRESENTATIONS (continued)

141. Chairman, International Board, Sixth International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, December 1992.

142. Co-Chairman, Session on Therapy of Rheumatic Diseases, Sixth International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, December 1992.

143. "NSAID Gastropathy, A World Class Problem: Why It Won't Go Away", Presented at the Machtay Memorial Lecture, Sixth International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, December 1992.

144. "New Strategies in Arthritis Therapy". Presented at the Sixth International Seminar on the Treatment of Rheumatic Diseases, Tel-Aviv, Israel, December, 1992.

145. "NSAID Gastropathy". Presented as an invitational lecture at the Technion Medical School, Haifa, Israel, December 1992.

146. Participant, U.S. Food and Drug Administration Arthritis Advisory Committee, Bethesda, Maryland, June 1993.

147. "Five Year Comparative Endoscopy Evaluation of Arthritis Patients Treated with Nabumetone Versus Naproxen", presented at the ILAR Annual Meeting in Barcelona, Spain, July 1993.

148. "Endoscopic Evaluation of the Effects of Diclofenac Sodium and Naproxen on the Upper Gastrointestinal Mucosa", presented at the ILAR Annual Meeting in Barcelona, Spain, July 1993.

149. "The Pro-Drug Concept of Nonsteroidal Anti-inflammatory Drug Therapy", presented as an invitational lecture at the ILAR Annual Meeting in Barcelona, Spain, July 1993.

150. Chairman: Opioid Therapy for Chronic Non-Malignant Pain: Clarifying the Controversy and Addressing the Practicality, San Antonio, Texas, November 1993.

151. President/Congress Chairman, 4th Biannual Congress of the International Society for Rheumatic Therapy, Chantilly, Virginia, May 1994.

152. "Industry Funding and Involvement", Presented at the 4th Biannual Congress of the International Society for Rheumatic Therapy, Chantilly, Virginia, May 1994.

153. Chairman, Antirheumatic Drug Guideline Breakout Session, Chantilly, Virginia, May 1994.

MEETINGS AND PRESENTATIONS (continued)

154. Co-Chairman/Speaker, Antirheumatic Drug Guideline Summary Presentation, Chantilly, Virginia, May 1994.
155. "Recent Developments in Analgesic Therapy for Osteoarthritis" Presented at the American College of Rheumatology, Minnesota, October 1994.
156. "Analgesic Drugs for Arthritis: Abuse or Underuse?", Anti-rheumatic Study Group, Minnesota, October 1994.
157. "Arthritis and Chronic Pain", Managing the Experience of Chronic Pain: A Multidisciplinary Approach Seminar, Scottsdale, AZ, March 3, 1995.
158. "Pharmacokinetic/Pharmacodynamic Relationships in Patients Receiving Controlled-Release Oxycodone" presented at American Society for Clinical Pharmacology and Therapeutics, 96th Annual Meeting, San Diego, CA, March 16, 1995.
159. "A Double-Blind, Randomized, Placebo-Controlled Designed Clinical Study to Compare the Safety and Efficacy of HYAL-AT2101 with Placebo Gel in the Treatment of Breakthrough Pain Associated with Osteoarthritis (OA) while on Stable Doses of NSAID Therapy" presented at Interscience World Conference on Inflammation, AntiRheumatics, Analgesics, Immunomodulators (INWIN), Geneva, Switzerland, March 28-30, 1995.
160. Chairman, Antirheumatic Drug Guidelines/ISRT Workshop, Scottsdale, Arizona, May 1995.
161. "Analgesic, NSAID and Cytoprotective Therapy" ISRT Symposium: Rheumatology in the HMO Era, Scottsdale, Arizona, May 1995.
162. Session Chairperson, "Introduction to Antirheumatic Drug Guidelines", Scottsdale, Arizona, May 1995.
163. Co-Chairperson, "NSAID Safety Issues: Alternative & Co-Medication Approaches", Scottsdale, Arizona, May 1995.
164. Co-Chairperson, "Pain & Arthritis: Whose Pain is it Anyway?", Scottsdale, Arizona, May 1995.
165. "Safety and Efficacy of Tramadol HCl in Breakthrough Osteoarthritis Pain". (poster presentation). The XIIIth European Congress of Rheumatology, Amsterdam, The Netherlands, June 18-23, 1995.

MEETINGS AND PRESENTATIONS (continued)

166 . "A Double-Blind, Randomized, Placebo-Controlled Designed Clinical Study to Compare the Safety and Efficacy of HYAL-AT2101 with Placebo Gel in the Treatment of Breakthrough Pain Associated with Osteoarthritis (OA) while on Stable Doses of NSAID Therapy" (poster presentation). The XIIIth European Congress of Rheumatology, Amsterdam, The Netherlands, June 18-23, 1995.

167. "Arthritis Therapy: Avoiding the Pitfalls", presented at the New Directions in Arthritis Therapy Seminar, Scottsdale, Arizona, October 18, 1995.

168. "Evaluation of Tramadol in Adjunctive Pain Therapy in OA", presented at American College of Rheumatology 59th National Meeting, San Francisco, California, October 21 - 26, 1995.

169. Co-Chairman/Speaker, New Approaches to the Arthritis Patient: Changes and Challenges for the Primary Care Physician, Phoenix, Arizona, November 1, 1995.

170. "The Effects of Controlled - Release (CR) Oxycodone on Pain Intensity and Activities in Patients with Pain Secondary to Osteoarthritis", presented at The 14th Annual Scientific Meeting of The American Pain Society, Los Angeles, California, November 9 - 12, 1995.

171. International Board Member, The Seventh International Seminar on The Treatment of Rheumatic Diseases, Israel, December 10 - 16, 1995.